# Clinical characteristics and in-hospital outcomes of acute decompensated heart failure patients with and without atrial fibrillation

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# Abstract

**Objective:** Atrial fibrillation (AF) and heart failure (HF) are common cardiovascular diseases. The impact of AF on in-hospital outcomes in acute decompensated heart failure (ADHF) is controversial. The aim of this study is to determine the prevalence of AF among hospitalized patients with ADHF and describe the clinical characteristics and in-hospital outcomes of these patients with and without AF.

**Methods:** We examined the multicenter, observational data from the real-life data of hospitalized patients with HF: Journey HF-TR study in Turkey that studied the clinical characteristics and in-hospital outcomes of hospitalized patients with ADHF between September 2015 and September 2016. **Results:** Of the 1,606 patients hospitalized with ADHF, 626 (39%) had a history of AF or developed new-onset AF during hospitalization. The patients with AF were older (71±12 vs. 65±13 years; p<0.001) and more likely to have a history of hypertension, valvular heart disease, and stroke. The AF patients were less likely to have coronary artery disease and diabetes. In-hospital adverse event rates and length of in-hospital stay were similar in ADHF patients, both with and without AF. In-hospital all-cause mortality rate was higher in patients with AF than in patients without AF, although the difference was not statistically significant (8.9% vs. 6.8%; p=0.121).

**Conclusion:** AF has been found in more than one-third of the patients hospitalized with ADHF, and it has varied clinical features and comorbidities. The presence of AF is not associated with increased adverse events or all-cause mortality during the hospitalization time. (Anatol J Cardiol 2020; 23: 260-7)

Keywords: atrial fibrillation, heart failure, hospitalization, mortality

# Introduction

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia and heart failure (HF) is an important cause of cardiovascular mortality (1, 2). The prevalence of AF and HF increases with age and often coexist (3). The coexistence of AF and HF is associated with an increased rehospitalization, morbidity, and mortality risk (4). AF directly causes the worsening of HF and

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also, the worsening of HF is an important risk factor for the development of AF (5, 6). HF is present in 34% of AF patients and AF is seen in 42% of HF patients (7, 8).

According to different studies, the short- and long-term prognostic importance of AF in patients with acute decompensated heart failure (ADHF) has been conflicting (4, 9-18). Several important studies have reported that the presence of AF in ADHF patients is associated with an increased risk of mortality (15, 17, 19). Whereas, some other studies noticed that the increased risk of mortality did not persist after adjusting other risk factors (14, 18, 20-24).

The aim of this study is to determine the prevalence of AF among hospitalized patients with ADHF and describe the clinical characteristics, management, and in-hospital outcomes of these patients with and without AF.

# **Methods**

# **Study population**

The Patient Journey in Hospital with HF in Turkish Population: Journey HF-TR study is a prospective, cross-sectional, multicenter, and observational trial that was conducted in intensive/ coronary care units (25). We enrolled a total number of 1.606 patients in 39 centers, in seven geographical regions of Turkey. The patients who were hospitalized with the diagnosis of ADHF in intensive/coronary care units between September 2015 and September 2016 were included in our study.

# Definitions

The Journey HF-TR study design, method details, and baseline data have been previously reported (25). Briefly, ADHF was defined as the worsening of HF in patients with previous diagnosis and/or hospitalization for HF. The demographic and clinical characteristics, clinical history, symptoms and signs, initial emergency department evaluation, including electrocardiography (ECG), and subsequent in-hospital management of patients were recorded. The most recent echocardiographic data and laboratory results were collected. Complications, length of hospital stay, and in-hospital mortality rates were registered.

The patients with ADHF were divided into two groups based on their medical history and ECG records during admission and hospitalization period. AF group had patients with history of AF and presence of AF rhythm on admission or development of acute AF during the hospitalization period. Sinus rhythm (SR) group (patients without AF) constituted the patients with the presence of SR on presentation and during the hospitalization period without the history of AF.

#### **Statistical analysis**

Normally distributed continuous variables are reported as mean±standard deviation and abnormally distributed continuous variables are reported as median and interquartile range. One-sample Kolmogorov–Smirnov test was used to identify whether the distribution of variable was normal or not. Continuous variables were compared using the independent t test or Mann–Whitney U test. Categorical variables are reported as frequencies and percentages and compared using the  $\chi^2$  test. A two-sided p value of <0.05 was considered statistically significant. Analyses were performed using SPSS software (SPSS Inc., USA) for Windows, version 22.0.

This study was approved by the Ethics Committee of the Istanbul Haydarpaşa Numune Training and Research Hospital.

# Results

## **Patient characteristics**

The mean age of the study population was 67.8 years and 57.2% were men. Of the 1,606 patients admitted with ADHF in the Journey HF-TR study, 626 (39%) had AF at baseline and/or during the hospitalization period, and 980 (61%) did not have a history of AF at baseline and/or during the hospitalization period. Women were in larger proportion in the AF group compared with the SR group (51% vs. 37.4%; p<0.001), and the patients with AF were older than those presenting with SR (71.2 vs. 65.9 years; p<0.001). Patients with AF had more comorbidities, including hypertension, cerebrovascular disease, or transient ischemic attack, moderate-to-severe valvular heart disease, and chronic pulmonary disease; whereas, coronary artery disease, diabetes mellitus, dyslipidemia, and current smoking were significantly less common in the AF group. The prevalence of anemia and chronic kidney disease were similar in the two groups (Table 1).

#### **Clinical presentation**

The most common precipitant factors of worsening of HF were arrhythmias (48%) (mostly, AF with rapid ventricular response) and infection (32%) for patients with AF, and infection (26%) and acute ischemia (23%) for patients with SR. On admission, the patients with AF were more symptomatic than those presenting with SR. Also, they had higher resting heart rates (102 bpm vs. 88 bpm; p<0.001), higher left ventricular ejection fraction (LVEF) (34% vs. 32%; p=0.008), and higher fasting blood glucose levels (Table 1). Systolic blood pressure, hemoglobulin and proB-NP levels (7,895 pg/mL vs. 8,022 pg/mL; p=0.150), and left bundle branch block on ECG were similar in the two groups. The prevalence of HF with preserved ejection fraction (HFpEF) was found to be higher in the AF group (24.6% vs. 11.5%; p<0.001).

#### Treatment

Before hospital admission, the patients with AF were more likely to be on treatment with diuretics and digoxin. Treatment rate with  $\beta$ -blockers (BB) was above 70% and that with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) was above 60% for patients of both AF and SR groups. ACEi or ARB, BB, and mineralocorticoid receptor antagonists (MRAs) were similarly used in the two groups (Table 2).

Variables	HF without AF	HF with current or a history of AF	<i>P</i> value
	(n=980)	(n=626)	
Age, y	65.9±13.4	71.2±12.2	<0.001
Female sex, n (%)	366 (37.4)	319 (51)	<0.001
<i>De novo</i> heart failure, n (%)	209 (21.3)	98 (15.6)	0.005
HFpEF, n (%)	112 (11.5)	154 (24.6)	<0.001
Heart rate, bpm	88.7±20	102.1±26.4	<0.001
Systolic BP, mm Hg	128.3±31.8	126.3±29.2	0.199
NYHA class III-IV, n (%)	687 (70.1)	522 (83.4)	<0.001
Dyspnea at rest, n (%)	490 (50)	466 (74.5)	0.001
Dyspnea with activity, n (%)	910 (92.9)	593 (94.7)	0.135
Orthopnea, n (%)	729 (74.4)	507 (81)	0.002
PND, n (%)	546 (55.7)	433 (69.1)	<0.001
Peripheral edema, n (%)	606 (61.8)	458 (73.2)	<0.001
Pleural effusion, n (%)	493 (50.3)	329 (52.6)	0.379
Ascites, n (%)	249 (25.4)	208 (33.2)	<0.001
HJR, n (%)	240 (24.5)	264 (42.1)	<0.001
CAD, n (%)	646 (65.9)	312 (49.9)	<0.001
Hypertension, n (%)	635 (64.8)	438 (69.9)	0.032
Diabetes, n (%)	438 (44.7)	233 (37.3)	0.003
Hyperlipidemia, n (%)	303 (31)	151 (24.2)	0.003
Previous stroke, n (%)	72 (7.3)	104 (16.6)	<0.001
CKD, n (%)	284 (29)	169 (27)	0.389
Anemia, n (%)	551 (56.2)	362 (57.9)	0.527
Smoking, n (%)	280 (28.6)	136 (21.7)	0.002
Device therapy, n (%)	53 (5.4)	29 (4.6)	0.491
LBBB, n (%)	201 (20.5)	130 (20.7)	0.901
Creatinine, mg/dL	1.46±2.5	1.27±0.7	0.064
GFR (mL/min/1.73 m <sup>2</sup> )	48.2±30.8	51.1±30.2	0.064
Fasting blood glucose, mg/dL	152.1±86.3	134.6±69.1	<0.001
Hemoglobin, mg/dL	12.2±2.2	12.1±2.1	0.366
NT-proBNP, pg/mL	8022±2021	7895±1103	0.150
LVEF, %	32.0±12.6	33.9±16.1	0.008
Moderate-to-severe MR, n (%)	440 (44.9)	334 (53.3)	<0.001
Moderate-to-severe TR, n (%)	385 (39.3)	346 (55.2)	<0.001
Moderate-to-severe AS, n (%)	43 (4.4)	48 (7.7)	0.006

 Table 1. Baseline patient characteristics and physical examination findings on admission

AS - indicates aortic stenosis; BP - blood pressure; CAD - coronary artery disease; CKD - chronic kidney disease; GFR - glomerular filtration rate; HFpEF - heart failure with preserved ejection fraction; HJR - hepatojugular reflux; LBBB - left bundle branch block; LVEF - left ventricular ejection fraction; MR - mitral regurgitation; NYHA - New York Heart Association; NT-proBNP - N-terminal pro–B-type natriuretic peptide; PND - paroxysmal nocturnal dyspnea; TR - tricuspid regurgitation

#### Discharge

On discharge, the patients with AF had significantly lower systolic blood pressure level (101 mm Hg vs. 108 mm Hg; p<0.001) and higher proBNP level (4.312 pg/mL vs. 2.235 pg/mL; p<0.001).

Heart rates on discharge were similar in the groups (Table 3). The patients with AF were more likely to be on treatment with diuretics, digoxin, and MRA. The treatment rate with BB and ACEi/ARB was similar for the two groups (Table 2).

	HF without AF (n=980)	HF with current or a history of AF (n=626)	<i>P</i> value
Baseline heart failure medications			
ACE/ARB inhibitors, n (%)	602 (61.5)	386 (61.7)	0.926
Beta – blockers, n (%)	695 (70.9)	464 (74.1)	0.162
MRA, n (%)	382 (39)	239 (38.1)	0.748
Diuretics, n (%)	660 (67.3)	483 (77.2)	<0.001
Digoxin, n (%)	120 (12.2)	213 (34.1)	<0.001
Discharge heart failure medications			
ACE/ARB inhibitors, n (%)	710 (72.4)	429 (68.5)	0.092
Beta – blockers, n (%)	795 (81.1)	500 (79.9)	0.536
MRA, n (%)	494 (50.4)	352 (56.3)	0.020
Diuretics, n (%)	660 (67.3)	483 (77.2)	<0.001
Digoxin, n (%)	120 (12.2)	212 (33.8)	<0.001

	HF without AF (n=980)	HF with current or a history of AF (n=626)	<i>P</i> value
Baseline			
Heart rate, bpm	88.7±20	102.1±26.4	<0.001
Systolic BP, mm Hg	128.3±31.8	126.3±29.2	0.205
NYHA class III-IV, n (%)	687 (70.1)	522 (83.4)	<0.001
NT-proBNP, pg/mL	8022±2021	7895±1103	0.150
Discharge			
Heart rate, bpm	70.8±20.4	72.6±27.4	0.133
Systolic BP, mm Hg	108.6±31.9	101.8±39.1	<0.001
NYHA class III-IV, n (%)	148 (15.1)	115 (18.4)	0.084
NT-proBNP, pg/mL	2235±449	4312±758	<0.001

BP - indicates blood pressure; NYHA - New York Heart Association; NT-proBNP - N-terminal pro-B-type natriuretic peptide; HF - heart failure; AF - atrial fibrillation

#### **In-hospital outcomes**

In-hospital adverse events, including pulmonary edema, cardiogenic shock, acute renal failure requiring renal replacement therapy, acute respiratory failure requiring noninvasive/invasive mechanical ventilation, or hemodynamic deterioration requiring invasive hemodynamic monitoring, occurred similarly in the groups with and without AF. The length of stay in the intensive/ coronary care unit was 4 days for both groups. All-cause in-hospital mortality rate was 7.6% and in-hospital mortality rate was higher in the AF group. (8.9% vs. 6.8%; p=0.121) (Table 4).

# Discussion

Our study showed high prevalence of AF among patients with ADHF and revealed significant differences in the demographic and clinical characteristics of ADHF patients with and without AF. Additionally, the present study provides information about the in-hospital adverse events, length of hospital stay, and in-hospital mortality rate of ADHF patients with and without AF.

The prevalence of AF varies between different HF studies. The AF prevalence has been reported to be 13–27% in chronic

	HF without AF (n=980)	HF with current or a history of AF (n=626)	<i>P</i> value
Pulmonary edema, n (%)	111 (11.3)	73 (11.6)	0.837
Cardiogenic shock, n (%)	33 (3.4)	21 (3.3)	0.989
NIMV, n (%)	154 (15.7)	110 (17.6)	0.327
IMV, n (%)	72 (7.3)	54 (8.6)	0.352
Length of ICU/CCU stay, days	4	4	0.980
Length of hospital stay, days	8	9	0.814
In-hospital mortality, n (%)	67 (6.8)	56 (8.9)	0.121

Table 4. Clinical event rates during intensive or coronary care unit stay and in-hospital outcomes of patients with and

HF patients (20, 26-28). This rate varies between 30% and 44% in the studies including ADHF patients (15-17, 24, 29-31). The prevalence of AF has increased with aging of the general population (32). According to the results of the Worcester Heart Failure study, AF prevalence in patients with HF in 1995 was 34.5%, which increased to 41.6% in 2004 (15). In our study, the prevalence of AF was 39% in patients with ADHF, which is similar to the rates reported in the ASCEND-HF (38.2%), EHFS II (38.7%), ATTEND (39.6%), and Worcester Heart Failure (39.7%) studies but higher than the rates reported in the ADHERE and OPTIMIZE-HF studies (15, 16, 24, 29, 31, 33). Meanwhile, the studies conducted in the Middle East region and Africa have reported AF prevalence rates between 14% and 18.3%, which is different from that reported in the studies conducted in the Western countries (34, 35). Older HF patients in the studies from the Western countries may explain this significant difference in the AF prevalence between these studies. In the studies in which the prevalence of AF in HF patients was >35%, the mean age of the population varied between 67 and 72 years (16, 29-31). However, in the studies in which the prevalence of AF in HF patients was <20%, such as Gulf CARE registry and THESUS-HF study, the mean age was 59 and 52.3 years, respectively (34, 35). Fibrosis in the atrium myocardium increases with age, thereby increasing the risk of AF development due to the structural and electrical remodeling (4). While AF prevalence is <0.5% under the age of 40 years, it increases up to 15% over the age of 80 years (36). As expected, in our study, the patients with AF were older than those without AF.

There is a "chicken or egg" relation between AF and HF due to many shared pathophysiological mechanisms. Based on the close interaction between these two clinical conditions, AF can develop as a result of HF and AF can also cause HF or worsen the existing HF (32). Therefore, the clinical presentation of ADHF patients with AF may be different compared with that of patients with SR. According to our study results, ADHF patients with AF are more symptomatic than patients with SR. The symptomatic status in ADHF patients with AF can be explained by the

decreased cardiac output and/or elevated left ventricular filling pressure due to the loss of atrial contribution to the left ventricular active filling (37). On the other hand, atrial dilatation is an important risk factor for AF development (32). In HF patients with dilated left atrium and AF, the pulmonary congestion and edema are more frequent due to the elevated left atrium pressure. This fact explains why the patients are more dyspneic at rest than during physical activity. In HF patients, tachycardia is another factor that worsens the symptoms and HF. Tachycardia-a poor prognostic factor in HF patients-enhances sympathetic system activation, disrupts coronary perfusion by shortening the diastole duration, increases workload and oxygen consumption of the heart, and leads to pulmonary congestion by causing increased left ventricular filling pressure (38). In our study, the patients with AF showed greater frequency of tachycardia than those with SR at the time of first admission. All these pathophysiological mechanisms mentioned above may explain the higher rates of symptomatic status in ADHF patients with AF than in those without AF.

The HF presentation can become more complex in the presence of hypertension, valvular heart disease, or COPD, which are the common risk factors for both HF and AF. Similar to the Worcester Heart Failure study, our results showed that the comorbidities, including hypertension, valvular heart disease, and COPD, which are related to the development and/or presence of AF, were more prevalent in ADHF patients with AF (15). Ischemic stroke and/or transient ischemic attack, which occur as a complication of AF, were significantly more common in ADHF patients with AF.

Interestingly, we noted a lower rate of diabetes in ADHF patients with AF than in patients with SR. As mentioned earlier, the increased AF prevalence is associated with the age of the general population. Other important mechanisms which are related to the increased AF prevalence are metabolic syndrome, obesity, and diabetes (32). AF is more common in diabetic patients than nondiabetic patients, and diabetes is a well-known risk factor for AF development (39). According to Nichols et al. (40), the AF frequency was significantly higher in diabetic patients, and the presence of diabetes was an independent risk factor for AF development in women. Despite the strong evidence regarding the association between diabetes and AF development risk, a significant portion of HF studies have found lower diabetes prevalence in HF patients with AF than those with SR (15–17, 21, 22). In a recent study investigating the ethnic differences in HF patients with AF reported that Asian HF patients with AF were older and showed higher rates of HT, stroke, and COPD and lower rates of diabetes, which were similar to our study results. The authors regarded this condition a "diabetes–AF paradox" and suggested that diabetes is a protector of left atrium remodeling and that it can be associated with a lower risk of AF development (41, 42).

The GWTG-HF study showed higher HFpEF prevalence and LVEF values in ADHF patients with AF than in patients with SR (17). In our study, HFpEF prevalence in ADHF patients with AF was significantly higher, which was consistent with the previous reports. The higher HFpEF prevalence is one of the key reasons for higher LVEF values in ADHF patients with AF than those with SR.

There was no difference between patients with and without AF in terms of the use of evidence-based HF medical treatments, including ACEi/ARB, BB, and MRAs, on admission; however, the use of diuretic and digoxin was higher in ADHF patients with AF than those with SR. As the patients with AF showed more apparent symptoms and hypervolemic findings, such as peripheral edema, ascites, or hepatojuguler reflux during physical examination, the use of diuretic treatment was higher in this group. Similarly, the rate of digoxin use may have been higher in patients with AF for establishment of heart rate control.

The in-hospital mortality rates vary between 3.8% and 9.3% in the studies including ADHF patients (21, 22, 24, 29-31, 34, 35). In our study, the in-hospital mortality rate was 7.6%. This rate is higher than the rates reported in the EHFS II and ESC-HF Pilot studies (6.7% and 3.8%, respectively) (30, 31). Compared with other European studies, the higher mortality rates in this study may be because the patients included in this study were more symptomatic and tachycardic. In our study, dyspnea incidence at rest and basal heart rate, which are the indicators of mortality and poor prognosis in HF, were higher than those reported in other studies. Moreover, a 10% decrease in the ejection fraction (EF) values in patients with HF with reduced ejection fraction (HFrEF) adversely affects prognosis and increases the all-cause mortality risk by 39% (43). Mean LVEF in our study was 33%, while that reported in the EHFS II and ESC-HF Pilot studies was 38% (30, 31). The lower mean EF value in our study may be one of the reasons for high in-hospital mortality. Additionally, we speculate that another important cause of high in-hospital mortality is the low usage rate of HF medications during hospital admission. At the time of hospital admission, approximately 60% of the patients were using ACEi/ARB, 70% were using BB, and only 40% were using MRAs. These HF medication usage rates were lower than those in other European and American studies. According to our

study, we think that the inadequate use of guideline-directed medical therapy prior to hospitalization is one of the most important reasons for a higher in-hospital mortality rate.

In ADHF patients, the impact of AF on in-hospital mortality remains unclear (22, 24, 29-31, 34, 35). In the ASCEND-HF study, the ADHF patients with AF showed significantly higher rates of all-cause mortality (2.6% vs. 1.7%, p=0.01), all-cause mortality on post-discharge day 30 (4.7% vs. 3.3%, p=0.005), and all-cause mortality on post-discharge day 180 (15.3% vs. 11.1%, p<0.001) than patients without AF; however, after modified analyses taking the confounding factors into account, this trend was disregarded. In modified analyses, the presence of AF was only associated with cumulative 30-day all-cause mortality and HF-caused hospitalization [HR, 1.19 (95% CI: 1.02-1.38), p=0.029] (16). In the OPTI-MIZE-HF study-a United States-based, multicenter, prospective study that included 48,612 ADHF patients and examined in-hospital mortality predictors-the in-hospital mortality rate was 3.8%. The in-hospital mortality predictors included advanced age, low SBP at the time of admission, low sodium levels, high heart rate, and increased creatinine levels. Pre-existing or new-onset AF was not an independent predictor of in-hospital mortality in HF patients (24). According to the results of the HEARTS registry. including 2,593 HF patients in the Middle East, the in-hospital mortality rate was 6.4%, and there was no difference between the patients with and without AF in terms of in-hospital mortality rates (6.7% vs. 6.3%, NS) (21). In another study examining the effects of AF on mortality in ambulatory HF patients under optimal medical treatment, 4,048 patients were included and followed up for 28 months on an average. According to univariate analyses, AF patients showed increased mortality compared to patients with SR. However, adjusted multivariate analysis revealed that AF was not associated with increased mortality rate (18).

The Worcester Heart Failure study including 9,748 ADHF patients found higher in-hospital and post-discharge (1 and 2 years after discharge) mortality rates in patients with pre-existing or new-onset AF than in patients without AF; this result is contrary to those reported in other similar studies. Corrections based on the factors affecting prognosis revealed ~70% increase in the in-hospital mortality risk, particularly for new-onset AF [OR, 1.66 (95% CI: 1.22-2.27)] (15). In a study examining the effects of AF on adverse events in 23,644 patients with HFpEF and HFrEF, the AF prevalence was 48.3%. Multivariate analyses revealed that the pre-existing or new-onset AF was independently associated with increased ischemic stroke, HF-related hospitalization, allcause hospitalization, and mortality; these trends were similar for both HFpEF and HFrEF patients (19). In the GWTG-HF study, 99,810 ADHF patients from 255 centers were evaluated and the effects of different AF types on adverse events were examined. The in-hospital mortality rates were significantly higher in patients with current AF, pre-existing AF, or new-onset AF than in patients with SR. Similar results were obtained for all three AF types in modified analyses (17). A recently published study demonstrated that AF is associated with increased all-cause mortality in patients with ADHF. Nonetheless, mechanistic link for the presence of AF and increased in-hospital mortality remained significant only in patients with HFpEF, but not in patients with HFrEF (44). Analysis of three randomized trials showed that the history of AF is associated with less loss of weight and decrease in NT-proBNP levels, but there is no association between the presence of AF and all-cause mortality (45).

In our study, in-hospital all-cause mortality rate was higher in patients with AF than in patients without AF, although the difference was not statistically significant.

#### **Study limitations**

The main limitation of our study is its observational design, which may lead to bias due to uncontrolled demographic and clinical variables. Thus, the study population may not represent the general population. Another important limitation of our study is the lack of data about AF types. We could not distinguish the impact of AF types (i.e., permanent AF, persistent AF, or paroxysmal AF) on in-hospital length of stay, adverse events, or all-cause mortality rates. The ADHF patients with subclinical AF may be underrepresented in AF group due to the lack of continuous rhythm monitoring, and this limitation may lead to underestimation of AF incidence in our study population. Registry data were based on documentation of medical history and management during hospitalization, and follow-up data were not obtained. Therefore, the readmission and mortality rates of the patients after discharge are unknown. Because of these several limitations, the results of this study have to be interpreted carefully.

# Conclusion

AF is present in more than one-third of the patients who were hospitalized with ADHF. Patients with ADHF and AF differed from those ADHF patients without AF in their age, gender, symptomatic status, LVEF, and comorbidities, such as hypertension, cerebrovascular disease, and valvular heart disease. Despite these differences, the presence of AF is not associated with increased adverse events or all-cause mortality during the hospitalization period in patients with ADHF.

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